

### Remarks

Applicants herewith amend claim 38 and add new claim 57. Thus, with the entry of this amendment, claims 36-45, 56 and 57 will be active in this case. Applicants respectfully request the Examiner to enter the above amendment as it re-organizes the claimed subject matter to correct a technical error and to better present this case for appeal. For instance, claim 38, which depends from claim 36, includes the recitations of lymphomas and leukemias, whereas claim 36 had previously been amended to delete cancers. Because leukemia and lymphoma are types of cancer, this dependency is improper. This inconsistency was inadvertently overlooked by the applicants and the Examiner in the last office action and applicants wish to correct this inconsistency now. Applicants also wish to add new claim 57 to specifically claim methods of treating lymphomas and leukemias so as to clarify the issues in this case and present a better appeal. Applicants understand that entry of the amendment after a final office action is within the Examiner's discretion and ask the Examiner to exercise this discretion in their favor as they enter the appeal process for the second time.

#### **I. REJECTIONS MAINTAINED UNDER 35 USC § 103**

##### **A. Claims 36-45 and 56 over The Hypericum Homepage in view of The Merck Manual**

The Examiner maintains that the Hypericum Home Page ("HHP") teaches that extracts of St. John's Wort, which contains hyperforin and hypericin, exhibits anti-inflammatory and antibacterial effects when applied externally or topically and specifically teaches that hyperforin is attributed with anti-inflammatory and antibacterial effects. The Examiner has argued that although HHP does not teach a method for treating an inflammatory condition with the claimed effective amounts or for the specific conditions, it would have been obvious to one of ordinary skill in the art to use hyperforin and/or hyperforin and hypericin to treat inflammatory conditions because of the disclosed anti-inflammatory effects.

The Examiner has further argued that it would have been obvious to one of ordinary skill in the art to optimize effective volumes and concentrations as a matter of routine experimentation and that it would have been obvious to one of skill in the art to include a pharmaceutical carrier.

Finally, the Examiner has also asserted that one of ordinary skill in the art would have been motivated to use hyperforin in a method for treating inflammatory conditions with a reasonable expectation of success because of hyperforin's known benefits, as disclosed by HHP. The Examiner relied upon the *Merck Manual* ("Merck") and Shroot *et al.* (U.S. Patent No. 5,151,534) and Lacefield *et al.* (U.S. Patent No. 4,021,553) as evidence that one of ordinary skill in the art would have known that eczemas are inflammatory diseases. According to the Examiner, one of ordinary skill in the art would have been motivated to combine HHP and Merck, and utilize hyperforin in a method for treating inflammation and eczemas with a reasonable expectation of success.

Applicants acknowledge the Examiner's follow-up discussion regarding the HHP reference's qualifications as prior art. However, applicants continue to challenge the merits of the rejection. As stated previously, St. John's Wort extract is not the same thing as hyperforin or hyperforin with hypericin. HHP discusses St. John's Wort extract. Specifically, it states that St. John's Wort contains at least ten different components. It describes some of the therapeutic uses of St. John's Wort, including the use for treating depression. It notes that it has been reported that externally applied St. John's Wort has anti-inflammatory and antibacterial effects and that such effect has been attributed to the hyperforin in the St. John's Wort extract. Chavez states that "[t]he chemical constituents of St. John's Wort are complex, numerous and diverse" and that "[t]he amount of the constituents is related to the harvesting period, the drying process and the storage." (Chavez at 1622) Although HHP mentions hyperforin as possibly being responsible for St. John's Wort having an anti-inflammatory property when used externally, it does not teach the use of a purified, effective amount of hyperforin in a pharmaceutical composition for use in treating the conditions recited in claim 36 and claims dependent therefrom. The Examiner admits these deficiencies but relies upon

what would be "obvious to the skilled artisan to optimize the effective amount and put it into a carrier" to complete her case.

In fact, the Examiner has asserted that "...at the time of the claimed invention, it would have been obvious to one of ordinary skill in art to optimize effective volumes and concentration as a matter of routine experimentation" and that one "would have been motivated to use hyperforin in a method of treating anti-inflammatory conditions with a reasonable expectation of success because of its known benefit as disclosed by HHP." The legal standard is that a showing of motivation requires more than a blanket assertion of motivation without anything more.

Also as asserted previously, applicants argue that the Examiner's reliance upon Merck and the other secondary references does not cure the limitations in the HHP reference. These secondary references disclose various types of inflammatory skin disorders, *e.g.*, eczema, lichen simplex, chronic dermatitis. The Examiner asks us to assume that a treatment of inflammation of one type would be a treatment for an inflammation of another type. This simply isn't true. Even if the HHP reference disclosed the use of hyperforin in a pharmaceutical to treat inflammation from a skin disorder, (which it does not), there is no scientific reason to believe such treatment would be suitable for the specific disorders listed in claim 36 and in the rejected dependent claims. The Examiner has failed to support the assumption that all substances that have anti-inflammatory properties are effective and safe for treating specific diseases that produce an anti-inflammatory response. Thus, one of skill in the art would not have an expectation of success based upon the Examiner's selected combination of teachings.

**B. Claims 36, 38-45, and 56 would not have been rendered obvious over Valavichyus within the meaning of 35 U.S.C. § 103(a).**

The Examiner maintains that Valavichyus "Antitumor Activity of Medicinal Plants from the Lithuanian SSR, USSR 6, Common St. John's Wort *Chamomilla Recutita*" (892- document U (translation)) teaches that extracts of St. John's Wort, specifically oil extracts, inhibit growth of sarcoma cells and tumor growth in animals. The Examiner

further maintains that it was well known in the art that oil preparations of St. John's Wort are hypericin-free and contain high concentrations of hyperforin, citing Chavez, *Monographs on Alternative Therapies in Hospital Pharmacy* 32: (12): 1621-1632 (1997) and that plant oils were used as pharmaceutical carriers.

Applicants traverse this rejection of the previously presented, amended claim 38 and new claim 57 for reasons already set forth in the record. With regard to new claim 57, which is directed to methods of treating lymphoma or leukemia, nothing in the art suggests treating these specific conditions.

Applicants again point out, however, that even if Valavichyus suggests oil extracts generally, such extracts, without more information are not pharmaceutically effective. The science presented in the specification shows that oil extracts of St. John's Wort is undesirable. The specification shows that actual skin cells (not a culture of cells many generations removed from the reality of disease processes in humans) were studied directly. That is, when applicants treated real skin of living humans, and then studied cell samples scraped from those subjects, the plant oil (St. John's Wort oil) failed miserably and clearly was shown to be a bad carrier. (Specification at 19, last paragraph through the middle of page 20)

This data is highly relevant. Applicants obtained data from real *in vivo* studies that shows that Valavichyus' conclusions are wrong. A skilled artisan following Valavichyus would be led in the wrong direction. To the extent Valavichyus is relevant, it shows teaching away from the claimed invention. Such evidence of leading away is a further indication of unobviousness.

Applicants reiterate that the specification provides ample information regarding the desirable aspects of pharmaceutically effective carriers. As described in the specification (see Example 11 and associated text) St. John's Wort oil is not a pharmaceutically effective carrier. In the context of Appellants' specification, which teaches how to use the claimed invention, there is no reason to think that plant oils *per se* somehow are pharmaceutically acceptable carriers. On the contrary, the oil studied (St. John's Wort) was not acceptable and it was found that the active ingredients can be

combined with ethanol and cream, as described on page 6 first paragraph, ethanol and greasy ointment base (second paragraph of page 6). Ethanol is particularly useful for the pharmaceutically effective carrier (page 8, second paragraph) and "plant extracts" such as plant oils, if used, are used as ingredients, not carriers *per se*, as mentioned on page 8 lines 19-22. Crude plant oil extracts generally are not pharmaceutically acceptable. The specification at pages 8 and 9 describes carriers that are acceptable. Plant oil extracts are not in this list.

The Examiner's assumption that it was also known in the art that plant oils were used as pharmaceutical carriers is simply not correct. A pharmaceutically acceptable carrier is not a plant oil extract. In fact, as discussed above, the specification provides data showing that a plant oil extract studied was not acceptable and that the plant oil has to be blended with acceptable materials (Specification at page 9, first three full paragraphs and Example 11).

Appellants further maintain that the above discussed data in the specification bolster the non-obviousness of their invention. Even if the PTO had presented a *prima facie* case of obviousness, the evidence presented in the specification would rebut such case. The claimed compositions (not with the plant oil as carrier but with an acceptable carrier) exhibited highly beneficial activity as unexpected results in comparison with the "natural" product promoted and taught by Valavichyus (and HHP.) These unexpected results are strong evidence of unobviousness.

**C. Claims 36, 38-45 and 56 would not have been obvious over Valavichyus in view of HHP and/or DeCosterd within the meaning of 35 U.S.C. § 103(a).**

The Examiner maintains the rejection of all the claims as being obvious over Valavichyus in view of HHP or DeCosterd, the secondary references being cited for allegedly teaching that extracts of St. John's Wort have anti-tumor properties. Specifically, the Examiner has argued that that DeCosterd teaches extracts of Hypericum inhibit growth of colon carcinomas and further teaches derivatives of hyperforin exhibit the growth-inhibiting activity. From this, the Examiner concluded that

at the time of the invention, hyperforin, derivatives thereof and extracts of Hypericum were well known as effective agents against cancer of various kinds.

Appellants again traverse this rejection as it may apply to the previously presented claims, amended claims 38 and new claim 57. Nothing in DeCosterd cures the deficiencies in the Examiner's case, as set forth above in connection with the discussion of HHP and Valavichyus. DeCosterd teaches the isolation of two new compounds, hyperevolutin A and hyperevolutin B from the root bark of Hypericum revolutin VAHL. These compounds showed growth inhibitory activity against *in vitro* colon carcinoma cell line. Such a report does not direct the skilled artisan to Applicants' invention. Rather, it invites experimentation and further investigation. As such, it does not support an obviousness rejection.

With regard to new claim 57, which is directed to methods of treating lymphoma or leukemia, nothing in the cited art would suggest such invention. The fact that the art invites experimentation in treating other types of cancer does not meet the standard for rendering this claimed invention obvious. Withdrawal of this rejection is respectfully requested.

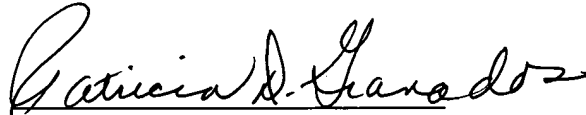
### CONCLUSION

It is respectfully requested that the above amendment be entered, that the rejections be withdrawn and the remaining claims be allowed. Early notification of allowance is respectfully requested.

Respectfully submitted,

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